Graduate Research Symposium 2026

Presentation Abstracts

Session 1

9:30-10:45

Give it your best Shot: How Spectraplakins Drive Dendrite Arbor Repair

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Dendrite injury occurs after nervous system traumas such as stroke or traumatic brain injury, and significant changes in dendrite structure have been documented in the contexts of neurodegenerative disease. Dendrites are vital to neuronal function, acting as antennae that receive signals from the surrounding environment or other neurons. Thus, maintaining or replacing this essential neuronal compartment may hold promise for the preservation or restoration of neuronal structure in disease. Short stop (shot), called MACF1 in mammals, has dual roles in dendrite maintenance and in neuronal injury responses. Shot promotes actin-microtubule crosslinking and dampens injury response signaling to maintain neuronal homeostasis. Shot/MACF1 exerts bimodal control of neuronal structure to not only promote dendrite arbor development but also constrain axon terminal branching and sprouting after injury. However, Shot/MACF1's role in dendrite maintenance and regeneration are unknown. Here, we use Drosophila sensory neurons and post-mitotic RNAi knockdown to show that (1) shot/MACF1 helps maintain dendrite arbors in a cell-type specific manner, (2) shot/MACF1 inhibits both canonical and non-canonical injury response pathways in uninjured neurons, (3) shot/MACF1 promotes dendrite regeneration across distinct cell types, and (4) shot/MACF1 protects against toxic human tau-induced dendrite arbor degeneration. Collectively, these findings establish shot as a key regulator of dendrite maintenance and repair and highlight shot/MACF1's translational relevance. In aged flies,

shot/MACF1 was recently shown to protect against axonal microtubule decay of CNS neurons in the adult Drosophila visual system. Our results corroborate these findings in dendrites at younger larval stages, and demonstrate a neuroprotective role for shot in neurodegenerative disease. Shot/MACF1's regulation of Wnt/ß-catenin signaling, GSK-3 signaling, and receptor tyrosine kinase signaling provide rich avenues for future research on the role of MACF1 in preserving or restoring dendrite architecture.

Digital Cognitive Phenotyping Identifies Imminent Risk in Preclinical Alzheimer's Disease

Casey Vanderlip, Grad Student
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As Alzheimer's disease (AD) diagnosis shifts toward biological definitions, clinicians increasingly encounter cognitively unimpaired individuals with elevated β-amyloid (Aβ). However, amyloid positivity alone provides limited insight into when cognitive decline will begin, complicating counseling, monitoring, and trial enrollment. We tested whether patterns of performance on a brief, self-administered digital cognitive assessment could be used to identify a high-risk cognitive phenotype that predicts imminent decline and tau progression in preclinical AD. We analyzed baseline digital cognitive performance in 1,146 Aβ+ and 538 Aβ− participants from the A4 and LEARN studies, followed for up to 4.6 years. Using unsupervised k-means clustering, we derived cognitive phenotypes from task-level performance across six computerized tasks. We evaluated associations with meaningful cognitive decline on the Preclinical Alzheimer's Cognitive Composite (PACC; ≥0.5 SD within-person decline), clinical progression, baseline tau PET burden, longitudinal tau accumulation, and plasma pTau-217 using Cox proportional hazards models and linear mixed-effects models. Clustering baseline digital cognitive performance split participants into four phenotypes. One phenotype, encompassing 18% of Aβ+ individuals, concentrated risk for rapid cognitive decline, clinical progression, and tau spread. Relative to Aβ− participants, this group experienced rapid cognitive decline, with a mean 240-week PACC decline of −4.11 points and nearly tripled risk of meaningful cognitive decline (HR 2.89; CI 2.26–3.77). Over follow-up, more than half progressed to mild cognitive impairment, corresponding to a nearly fivefold increase in hazard of clinical progression (HR 4.83; CI 3.61–6.44). This phenotype mapped directly onto AD biology, showing greater baseline medial temporal tau burden and accelerated neocortical tau accumulation over time. Plasma pTau-217 and the digital phenotype captured complementary risk signals; individuals positive for both exceeded a fourfold hazard of meaningful cognitive decline. Using a brief digital cognitive assessment, we identified a latent phenotype consisting of a subgroup of Aβ+, cognitively unimpaired individuals who are at disproportionately high risk for near-term cognitive decline and tau spread. When combined with plasma pTau-217, this scalable approach substantially improves prognostic precision, with direct implications for trial enrichment, monitoring strategies, and early therapeutic decision-making.

Harnessing Cyanobacterial Secondary Metabolites as Novel Drug Scaffolds

Marie-Désirée Schlemper-Scheidt, PostDoc
Avalon Lab Ecology and Evolutionary Biology

Natural products continue to represent a prolific source of structurally diverse and pharmacologically relevant compounds for drug discovery.[1] Since the 1970s, cyanobacteria have been recognized as rich producers of secondary metabolites exhibiting a broad spectrum of biological activities against human diseases.[1] This current study focuses on an environmental sample of cyanobacteria collected in the Republic of Cabo Verde in May 2023. The organic extract was subjected to fractionation by normal phase medium pressure liquid chromatography. All fractions were evaluated using a panel of bioactivity assays. Several fractions showed activity against Trypanosoma brucei,

the etiologic agent of African sleeping sickness, as well as against Plasmodium spp., which cause malaria. Furthermore, the fractions were evaluated for anticancer activity in NCI H460 and D-283-med cell lines. Here, we present the bioactivity-guided isolation as well as the mass spectrometry and nuclear magnetic resonance-based elucidation of secondary metabolites from this Cabo Verdean cyanobacterial extract. Our findings highlight the therapeutic potential of marine cyanobacteria as a source of novel bioactive compounds and support continued exploration of underexplored marine ecosystems for natural product-based drug discovery.

UHRF1 as an epigenetic driver of tumorigenicity and immune evasion in triple negative breast cancer

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Benavente Lab Developmental and Cell Biology

Ubiquitin-like with PHD and RING Finger Domains 1 (UHRF1) is a multidomain epigenetic regulator essential for the maintenance of DNA methylation and repressive histone marks during cell division. As a downstream effector of the RB/E2F pathway, frequently deregulated in cancer, UHRF1 is aberrantly overexpressed in several malignancies, including triple-negative breast cancer (TNBC). Clinical datasets reveal that high UHRF1 expression correlates with poor overall survival in TNBC, underscoring its clinical relevance. Using CRISPR/Cas9-mediated gene editing, we demonstrate that UHRF1 loss significantly impairs TNBC cell tumorigenicity. UHRF1-deficient TNBC cells exhibited reduced clonogenicity, migration, and invasion in vitro. In orthotopic xenograft models, tumors with low UHRF1 expression displayed significantly reduced growth and metastatic potential compared to controls. Transcriptomic profiling revealed that UHRF1 loss led to widespread depression of immune-related genes, suggesting that UHRF1 orchestrates an epigenetically repressed, immune-evasive state. To validate these findings in an immunocompetent context, Uhrf1 knockout (KO) TNBC cell lines were generated from mouse 4T1 cells. Consistent with human models, Uhrf1 KO cells displayed reduced tumorigenic potential and formed significantly smaller tumors in Balb/cJ mice. Importantly, Uhrf1 KO tumors showed increased infiltration of activated cytotoxic T cells (CD8+ CD44hi) and plasmacytoid dendritic cells (pDCs), alongside a higher cytotoxic-to-regulatory T cell ration, indicating an enhanced anti-tumor immune landscape following loss of UHRF1-mediated repression. Together, these results establish UHRF1 as a master epigenetic regulator linking the RB/E2F axis to tumor progression and immune modulation in TNBC. Targeting UHRF1-dependent chromatin regulation may represent a promising strategy to simultaneously suppress tumor growth and overcome immune evasion in aggressive breast cancers.

A Tiny Chip Takes On Brain Cancer's Biggest Challenge

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Hughes Lab Developmental and Cell Biology

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor and remains associated with poor long-term survival, with a 5-year relative survival rate of 6.7%. Although many tumors initially respond to standard first-line therapy, including surgical resection, irradiation, and temozolomide (TMZ)-based chemotherapy, recurrence commonly occurs within 10 months of initial resection and continues to present a major therapeutic challenge. Current preclinical drug screening approaches often rely on traditional 2D culture systems that do not adequately recapitulate the human tumor microenvironment, potentially overlooking therapeutically relevant pathways and drug responses. To address this limitation, our work employs a state-of-the-art 3D in vitro GBM-on-a-chip culture system designed to better model GBM tumor–microenvironment interactions. This platform provides a more physiologically relevant approach for identifying targetable tumor- and microenvironment-directed pathways and for screening candidate therapies that may be missed using conventional 2D models. Overall,

the GBM-on-a-chip system offers a promising strategy to improve preclinical therapeutic discovery for recurrent GBM.

Session 2

1:00-2:15

A Deletion of Drak2 Induces Regulatory T Cell Differentiation via Metabolic Reprogramming of Fatty Acid β-Oxidation

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Walsh Lab Molecular Biology and Biochemistry

Multiple sclerosis (MS) is a neurodegenerative autoimmune disease caused by autoreactive T cells targeting neuronal myelin. There is a need for more targeted MS therapeutics, such as improving regulatory T cell (Treg) expansion and suppressive function. One regulating factor of Treg proliferation is metabolic reprogramming, which shifts how cells rely on metabolic pathways for energy post-activation. Tregs tend to be less glycolytic, favoring fatty acid β-oxidation (FAO) and oxidative phosphorylation (OXPHOS). Here, we identify the death-associated protein kinase-related apoptosis-inducing protein kinase 2 (DRAK2) as a target involved in metabolic reprogramming of FAO to drive conventional T cell (Tconv) vs. Treg expansion. A DRAK2 deficiency was previously implicated in resistance against experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. However, Treg depletion in DRAK2-deficient mice restored EAE sensitivity. We also found that Drak2-/- Tregs and Tconvs had upregulated lipid homeostasis that became normalized during FAO inhibition. Since myelin-reactive Drak2-/- Tregs are essential to EAE resistance, further understanding metabolic targets associated with DRAK2 can lead us towards T cell-targeted MS treatments.

Leveraging stem cell and chimeric modeling platforms to understand protective human microglia responses in the context of Alzheimer's disease

Ghazaleh Eskandari-Sedighi, PostDoc
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"Genome-wide association studies (GWAS), combined with data from human studies and mouse models, suggest that microglia play a significant role in Alzheimer's Disease (AD) susceptibility. Numerous studies have examined the responses of human microglia to amyloid pathology in vivo. However, AD is characterized by both amyloid and tau deposition. While some studies have investigated murine microglial responses to combined amyloid and tau pathologies, in vivo studies of human microglia have largely been limited to postmortem, end-stage analyses. Recent data from transgenic mice globally expressing the APOE3-R136S (Christchurch) variant, as well as observations from the human carrier of this gene, suggest that this variant disrupts the exacerbating influence of amyloid-accelerated tau pathogenesis. Moreover, these studies indicate that the protective responses associated with APOE3-R136S converge on microglia.

Leveraging our induced pluripotent stem cell-derived microglia (iMG) and chimeric mouse modeling platforms, we are investigating the protective human microglial responses associated with the APOE3-R136S variant in vivo. Specifically, we developed a novel xenotolerant chimeric mouse model of AD that develops both amyloid and tangle pathologies. Initial analysis on transplanted human microglia (xMG) in these mice highlighted unique responses of human xMG to combined pathologies in vivo. We then transplanted these mice with human xMG expressing APOE3-R136S or APOE3 to investigate how microglial APOE3-R136S expression skews human xMG responses in vivo.

We observed that combined amyloid and tau elicit a robust type-I interferon response in the xMG and drive increased formation of a distinct rod microglial phenotype these cells. Furthermore, we identified significant correlations between xMG morphological changes, neuronal loss, and tangle pathology. Finally, APOE3-R136S expression in xMG appears to ameliorate these detrimental responses.

Overall, our novel chimeric mouse model highlights how the presence of combined pathologies influences human xMG, emphasizing the need for novel animal models that can recapitulate AD more accurately."

Environmental Pollutant Benzo[a]pyrene Disrupts the Meiotic Spindle in Mouse Eggs

Kathleen Leon Parada, Grad Student
Luderer Lab Developmental and Cell Biology

Benzo[a]pyrene (BaP) is released as a by-product from the incomplete combustion of organic materials. Sources include combustion of tobacco/cannabis, fossil fuels, wood, or grilled foods. The finite pool of oocytes within the ovary is established from primordial germ cells (PGCs) during prenatal development. The Luderer laboratory demonstrated that prenatal exposure to BaP significantly reduced the number of germ cells, leading to premature ovarian failure, increased oxidative stress in surviving eggs, and reduced fertility in adulthood. The meiotic spindle consists of microtubules that attach to chromosome kinetochores to ensure that each egg receives half of the chromosome set in which euploidy is reestablished upon fertilization. The meiotic spindle plays a pivotal role in preserving egg quality and genetic integrity. We hypothesized prenatal exposure to BaP would significantly reduce the quantity and quality of surviving oocytes by disrupting spindle integrity. To test this hypothesis, we orally dosed pregnant F0 dams to 0, 0.033, or 2 mg/kg/day of BaP from 6.5-15.5 dpc. Eggs were collected from F1, post-natal day 35-45 mice. Spindle length, metaphase plate length, spindle volume, chromosome alignment, and ploidy were assessed using IMARIS software. The number of eggs collected from BaP-exposed mice did not differ from controls (GEE, $p>0.05$). Spindle length (GEE, $p=0.005$) and spindle volume (GEE, $p=0.002$) were significantly increased in BaP-exposed mice compared to control mice. Compared to control mice, percent aneuploidy was significantly higher in mice

exposed to 0.033 mg/kg/day BaP (Kruskal Wallis, p=0.034). Chromosome alignment and metaphase plate width was not altered by BaP exposure (GEE, p>0.05). Prenatal BaP exposure compromised egg quality by disrupting spindle characteristics that are implicated in reduced developmental competence. This exposure also undermines the genetic integrity of eggs at a human relevant dose, which raises an important question of BaP effects on long-term reproductive, maternal, and prenatal health.

Keeping the Peace: How Bacterial Capsules Stabilize Temperate Phage–Host Symbioses

Mirjam Zuend, PostDoc

Wiles Lab Molecular Biology and Biochemistry

Viruses that infect bacteria, called phages, are abundant in microbiomes, where they shape bacterial diversity, nutrient cycling, and community structure. Among them, temperate phages occupy a unique position: they can persist within bacterial hosts through lysogeny, integrating into the host genome, yet they can also switch to lytic replication and kill those same hosts. This dual lifestyle creates an inherent tension. Long-term coexistence requires a delicate balance in viral replication, as excessive killing risks host collapse, whereas excessive restraint limits viral spread. How this stability is maintained and what prevents phage-host relationships from collapsing during viral outbreaks remain unclear. To address this question, we experimentally disrupted the stability of a naturally co-evolved temperate phage-host system by repeatedly cycling phages through lytic and lysogenic replication while selecting for increased infectivity. Surprisingly, rather than evolving greater infectivity, the phage repeatedly selected for rare host variants lacking a protective surface capsule, thereby rendering them highly susceptible to infection. This recurrent outcome pointed to an unexpected role for bacterial surface structure in maintaining phage-host stability. Genetic and imaging-based analyses revealed that the bacterial capsule acts as a safeguard in the temperate phage-host relationship, simultaneously protecting host cells from lethal collateral phage attack among neighboring lysogens while promoting viral dispersal. As a result, bacterial capsules determine the extent to which phage outbreaks reshape microbial community composition. Overall, these findings uncover host-mediated feedback that stabilizes phage-host coexistence and shapes microbial community structure, offering new insight into how temperate phage-host symbioses persist despite recurrent viral outbreaks.

Mathematical and Mouse Models Identify T Regulatory Cell Influx as A Key Determinant of Acquired Resistance to PD-1 Immunotherapy

Rachel Sousa, Grad Student

Lowengrub Lab Systems Biology

The immune system can eradicate cancer, but various immunosuppressive mechanisms active within a tumor curb this beneficial response. However, unraveling the effects of multimodal interactions between tumor and immune cells and their contributions to tumor control using an experimental approach alone is time- and resource-intensive. To identify the critical immunological features associated with tumor control and escape, we built a mechanistic, structurally identifiable mathematical model of the interactions between CD8+ T cells, Tregs, DCs, and tumor cells deeply rooted in current biological concepts. A distinguishing feature of our model is that it captures Treg accrual occurring after checkpoint blockade immunotherapy. After successfully fitting the mathematical model to experimental data from an immunogenic melanoma mouse model that shows acquired resistance to PD-1 immunotherapy and ensuring that the model was practically identifiable, we generated hundreds of parameter sets, each of which fits the data well and represents a unique ‘virtual mouse’ to capture variability across individuals. Our model indicates that the initial tumor and immune conditions instruct cancer control or progression and that there exist optimal initial ratios of immune cells that result in improved tumor control. The model further

predicts that the Treg influx into the tumor is a key determinant of resistance to PD-1 immunotherapy. We validated all of these predictions experimentally. Overall, this integrated approach of modeling and experimental validation identified crucial determinants of resistance to PD-1 immunotherapy and can be used to guide the development of more effective therapeutic strategies.